High-intensity focused ultrasound for prostate cancer: a practice guideline

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Abstract

Objective: The aim of this practice guideline was to develop evidence-based recommendations for clinicians on the use of high-intensity focused ultrasound (HIFU) in patients with localized prostate cancer.

Methods: The guideline was developed using the methods of Cancer Care Ontario's Program in Evidence-Based Care (PEBC). The core methodology of the PEBC's guideline development process is systematic review. A comprehensive literature search was undertaken to identify high-quality studies, reviews and other practice guidelines on the use of HIFU in prostate cancer. The evidence formed the basis of the recommendations, which were reviewed and amended where necessary, by clinical experts in medical and radiation oncology and urology.

Results: The literature review yielded limited evidence. No randomized controlled trials or meta-analyses comparing HIFU with currently accepted management approaches were identified. The body of evidence is primarily based on data from case series. Internal feedback was provided by the PEBC Genitourinary Disease Site Group membership and the Report Approval Panel. External peer review included targeted review by clinical experts specifically requested to comment on the guideline, and professional consultation through an online survey of health care professionals.

Conclusion: HIFU is currently not recommended as an alternative to accepted curative treatment approaches for localized prostate cancer.

Résumé

Objectif : Le but de ce guide de pratique était d'élaborer des recommandations factuelles pour les cliniciens concernant l'emploi d'ultrasons ciblés de haute intensité (HIFU) dans le traitement du cancer de la prostate localisé.

Méthodologie : Le guide de pratique a été élaboré à l'aide de la méthodologie préconisée par Action Cancer Ontario dans son Programme de soins fondés sur la recherche (PSFR). La méthodologie centrale pour l'élaboration de lignes directrices selon ce programme repose sur un examen systématique. Des recherches exhaustives ont été effectuées dans les publications afin de cerner des études de haute qualité, des articles de synthèse et d'autres lignes directrices de pratique sur l'emploi de la technique HIFU dans le traitement du cancer de la prostate. Les données dégagées ont formé la base des recommandations, qui ont ensuite été examinées et modifiées, si nécessaire, par des cliniciens experts en oncologie médicale, en radio-oncologie et en urologie.

Résultats : La revue de la littérature n'a permis de dégager que des données limitées. Aucun essai clinique avec randomisation ni aucune méta-analyse comparant la technique HIFU à des techniques de traitement actuellement acceptées n'ont été cernés. L'ensemble des données est fondé surtout sur des séries de cas. Des commentaires internes provenaient des membres du groupe sur les maladies génito-urinaires du PSFR et du Comité d'approbation du rapport. L'examen externe par des pairs incluait un examen ciblé par des cliniciens experts à qui on avait demandé spécifiquement de commenter le guide de pratique, et par des professionnels de la santé par le biais de consultations professionnelles en ligne.

Conclusion : La technique HIFU n'est actuellement pas recommandée comme traitement de rechange aux techniques actuellement acceptées pour le traitement du cancer de la prostate localisé.

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Introduction

Carcinoma of the prostate is one of the most common malignancies to afflict men. The use of high-intensity focused ultrasound (HIFU) has recently been promoted as an alternative treatment for localized prostate cancer. Due to increasing patient interest and the current use of HIFU technology in Ontario, an evidence-based clinical practice guideline was needed to clarify the role of HIFU in the treatment of prostate cancer.

This clinical practice guideline was developed by the Genitourinary Disease Site Group (GU DSG) of Cancer Care Ontario's Program in Evidence-Based Care (PEBC), using the methods of the Practice Guidelines Development Cycle.[1] This practice guideline is a convenient and up-to-date source of the best available evidence on HIFU for prostate cancer. For this project, the core methodology used to develop the evidentiary base was the systematic review. Peer review by clinical experts in Ontario and throughout Canada also formed part of the guideline development process.

Based on a systematic review of the use of HIFU in prostate cancer,[2] draft recommendations were developed by consensus of the GU DSG to create this clinical practice guideline. The practice guideline and systematic review are intended to promote evidence-based practice in Ontario,

Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario.

Guideline question

In patients with localized prostate cancer, how does HIFU compare with currently accepted curative treatment approaches, such as radical prostatectomy, external beam radiotherapy and brachytherapy? Outcomes of interest include overall survival, biochemical failure, metastatic rate and adverse effects.

Methods

Guideline development

The PEBC is an initiative of the Ontario provincial cancer system – Cancer Care Ontario.[1] The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation and evaluation of evidence-based products designed to facilitate clinical, planning and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels to develop practice guidelines. These panels are comprised of clinicians, other health care providers and decision-makers, methodologists and community representatives from across the province.

A small committee made up of a subgroup of members of the GU DSG conducted a systematic review of the literature to inform the practice guideline. Evidence was selected by 2 members of the GU DSG and 1 methodologist. Recommendations on the use of HIFU in localized prostate cancer were drafted with input from the entire GU DSG. Prior to the submission of the draft report for external review, the report was reviewed by the PEBC Report Approval Panel, which consists of 2 members, including an oncologist, with expertise in clinical and methodology issues. No major issues were raised by the Report Approval Panel. Editorial suggestions were incorporated.

External review by Ontario clinicians

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts, and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the approval of the report by the PEBC Report Approval Panel, the GU DSG circulated the practice guideline and systematic review to external review participants for review and feedback.

During the guideline development process, 6 clinical or methodological experts from Ontario, Quebec and British Columbia were identified by the GU DSG. These experts were contacted by email and asked to serve as reviewers. Three reviewers agreed to participate in the review, and the draft report and a questionnaire were sent to them via email. The questionnaire consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The GU DSG reviewed the results of the questionnaire.

For the professional consultation component of the external review, feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Medical and radiation oncologists and surgeons working in the field of genitourinary cancer in Ontario were identified from the PEBC database and were contacted by email to inform them of the guideline and to solicit their feedback. Participants were asked to rate the overall quality of the practice guideline and whether they would use or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations and the evidentiary base.

Results

External review

Few suggestions for improving the guideline were generated during external review. The main points contained in the written comments were that caution is warranted with respect to the use of HIFU and that randomized controlled trials (RCTs) and studies with longer follow-up are needed.

Recommendation

HIFU cannot currently be recommended as an alternative to accepted curative treatment approaches for localized prostate cancer.

Qualifying statements

- HIFU should be considered an investigational treatment, with its use restricted to clinical trials, and to patients for whom other local treatment options are not suitable. Patients should be made aware of currently accepted curative treatment approaches for localized prostate cancer.
- Few RCTs exist that compare the efficacy of accepted curative treatments for localized prostate cancer to indicate the superiority of one approach over another.

However, each accepted curative approach has evolved as a standard treatment option based on mature clinical data from well-designed prospective studies. Recently, RCTs have been reported comparing cryoablation with external beam radiotherapy.[3,4] These studies have shown divergent results and the studies have several limitations. The key evidence on HIFU needs to be interpreted in light of limited information from RCTs comparing accepted curative treatments.

- The results from case series of HIFU require confirmation in well-designed prospective studies of sufficient size with appropriate (and validated) end points before HIFU can be considered a standard treatment option. The long natural history of prostate cancer necessitates a long length of patient follow-up to determine efficacy.
- The efficacy and toxicity associated with standard curative treatments administered post-HIFU are unknown.

Key evidence

A systematic review of the literature was performed and showed there is currently no RCT evidence comparing the efficacy of HIFU with accepted curative treatments for localized prostate cancer. The clinical evidence on HIFU is comprised of 34 case series (each containing a minimum of 50 patients).[5-50] Twenty-three series were published as full reports and 11 were published in abstract form.

- Across the 34 studies of HIFU, the number of patients treated ranged from 50 to 1234 and totalled 7438 patients. However, owing to multiple counting of patients among series, it is difficult to estimate the true total number of patients treated with HIFU.
- Most patients treated had localized prostate cancer (stage T1-T2) and underwent HIFU because they were unsuitable or unwilling to undergo surgery. Over 90% of patients were treated as primary therapy, and less than 10% of patients were treated as salvage therapy following radiotherapy failure. Gleason scores ranged from 2 to 10 (average was ≤7), mean initial PSA values ranged from 2.1 to 27.7 ng/mL, and mean prostate volumes ranged from 7.8 to 36.6 cc. The mean age range of patients was 65 to 74 years.
- HIFU was delivered by the Ablatherm devices (EDAP TMS, Lyon, France) in 27 series[7,36-50] and Sonoblate (Focus Surgery, Inc., Indianapolis, IN) in 7 series.[8-35] Most studies indicated the use of prototype devices and technical changes over the study course.
- The main outcomes reported in series were negative biopsy rates, prostate-specific antigen (PSA) levels (nadir, percent of patients with PSA ≤0.5 ng/mL), disease-free survival rates and adverse effects.
- The definition of "disease-free" and the time point of measurement of this outcome varied significantly among series, making comparisons difficult. The most common definition included a positive biopsy and/or 3 consecutive PSA rises after the PSA nadir.
- Other outcomes relevant to this review, overall survival (1 series) and metastatic rate (no series), were not frequently reported.

HIFU as primary treatment

- Twenty-nine studies, n = 6912.[5-42]
- Median patient follow-up ranged from 6 months to 6.4 years.
- Follow-up biopsies were usually performed 3 to 6 months post-HIFU. Negative biopsies ranged from 35% to 95.1% in 21 series.
- Five-year disease-free survival rates ranged from 55% to 95% in 5 series.
- The percentage of patients reaching a PSA nadir of ≤0.5 ng/mL ranged from 55% to 91% in 10 series; and mean PSA nadirs ranged from 0 ng/mL to 1.9 ng/mL in 17 series.
- Most patients were treated with HIFU alone. Re-treatment rates ranged from 7.7% to 43% in 11 series. Re-treatment was associated with increases in specific morbidities in 2 series that examined the effect of re-treatment.
- Some patients also received neoadjuvant hormonal therapy or transurethral resection of the prostate (TURP) prior to HIFU. Neoadjuvant hormonal therapy (range, 4% to 61% of patients in 12 series) was stopped prior to HIFU in all series. In 1 study that examined outcomes of HIFU combined with TURP, combined treatment was associated with similar efficacy, reduced catheter time and decreased morbidity and re-treatment rates compared with patients treated with HIFU alone.
- The common complications (medians) associated with HIFU included impotence (44% among previously potent patients), urinary tract infections (7.5% of patients), urethral stricture (12.3%), stenosis (7.8%), urinary incontinence (8.1%), urinary retention (5.3%), chronic perineal pain (3.4%) and urethrorectal fistula (1.0%).
- The percentage of patients requiring adjuvant or additional treatment (e.g., radiotherapy or hormonal therapy) after HIFU was reported in 5 series and ranged from 4% to 61%.
- The series (n = 140) with the longest follow-up (i.e., 6.4 years) reported a negative biopsy rate of 86.4% and a 5-year disease-free survival rate of 66%. Eight-year actuarial overall and cancer-specific survival rates were 83% and 98%, respectively. After HIFU, the mean PSA nadir was 0.62 ng/mL and a nadir of ≤0.5 ng/mL was reached in 68.4% of patients. The 5-year biochemical-free rate was 77%.

HIFU as salvage treatment

- Five studies, n = 512.[43-50]
- Only 5 series examined the efficacy of HIFU as salvage treatment for local recurrence after external beam radiotherapy.
- The largest series (n = 167) with the longest length of follow-up (18.1 months) reported a negative biopsy rate of 73% and a 5-year disease-free survival rate of 17%.
- A median PSA nadir of 0.19 ng/mL was reached within 3 months of HIFU.
- The adverse effects of treatment were urinary incontinence (50% of patients), bladder outlet obstruction (20%) and rectourethral fistula (3.0%).

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This paper has been peer-reviewed.

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